IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPLICATION OF	)	
	)	
YAAKOV NAPARSTEK	)	GROUP ART UNIT: 1644
	)	
SERIAL NUMBER: 09/826,069	)	EXAMINER: G. EWOLDT
	)	
FILED: APRIL 4, 2001	)	
	)	

TITLE: PEPTIDES FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS AND METHODS OF TREATING SYSTEMIC LUPUS ERYTHEMATOSUS

MAIL STOP APPEAL BRIEF – PATENTS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ON APPEAL FROM THE PRIMARY EXAMINER TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANT'S BRIEF UNDER 37 C.F.R. § 41.37

Sir:

The present Appeal Brief is submitted in support of the Notice of Appeal filed **June 16, 2009**.

TABLE OF CONTENTS

I

REAL PARTY IN INTEREST

The real party in interest for the application in this Appeal is assignee Hadasit Medical Research Services and Development Company LTD., by virtue of the Assignment dated July 18, 2001, recorded at Reel/Frame 012155/0252 on September 7, 2001, in the United States Patent and Trademark Office.

II

RELATED APPEALS AND INTERFERENCES

As the legal representative of Appellant, the undersigned attorney has no knowledge of any appeals or interferences directly related to this Appeal.

III

STATUS OF CLAIMS

Claims 8-13 of this patent application are pending. Claims 1-7 and 14 are cancelled. Claims 8-13 were finally rejected under 35 U.S.C. §103(a) in an Office Action mailed March 17, 2009 ("Final Office Action").

Six pending claims, Claims 8-13, are at issue in this Appeal. Claim 9 is independently patentable. Claim 11, while independent, stands or falls with Claim 9. Claims 8, 10, 12 and 13 also stand or fall with Claim 9.

IV

STATUS OF AMENDMENTS

No claims were amended after final rejection. A copy of the claims involved in this Appeal is contained in the Appendix attached hereto.

V
SUMMARY OF CLAIMED SUBJECT MATTER

In one embodiment set forth in Claim 9, Appellant has discovered a method of treating a subject having systemic lupus erythematosus (SLE) comprising extracorporeal treatment of plasma from the subject by affinity adsorption column chromatography, wherein the column comprises a peptide having an amino acid sequence as set forth in SEQ. ID. NO. 1, and returning plasma so treated to the subject.

See the specification at page 5 lines 3 – 11.

In another embodiment set forth in Claim 11, Appellant has discovered a method of treating a subject having systemic lupus erythematosus comprising extracorporeal treatment of plasma from the subject by affinity adsorption column chromatography, wherein the column consists essentially of a peptide having an amino acid sequence as set forth in SEQ. ID. NO. 1, and returning plasma so treated to the subject.

See the specification at page 5 lines 3 – 11.

The methods of the present invention satisfy a long-felt need in the treatment of SLE, by providing removal of lupus-specific antibodies only. Removal of only lupus-specific antibodies prevents the rebound effect, a common negative side effect in other methods of non-specific plasma treatment (plasmapheresis). The methods of the present invention also reduce the need for strong immunosuppressant drugs, with the attendant negative side effects, in the long-term treatment of SLE.

VI

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Has an alleged Prima Facie Case of Obviousness of Claims 8-13 Under 35 U.S.C. §103(a) over Gaubitz et al. (1993) ("Gaubitz") in view of U.S. 6,228,363 ("the '363 patent") and Madaio et al. (1996) ("Madaio"), Been Overcome, In View of the Evidence Of Lack Of Predictability Of Success, And Unexpected Results?

VII

ARGUMENT

Any Alleged Prima Facie Case of Obviousness under 35 U.S.C. §103(a) over Gaubitz in view of the '363 patent and Madaio Has Been Successfully Rebutted.

A. The Rejection

Claims 8-13 stand rejected under 35 U.S.C. § 103(a) as being obvious over Gaubitz in view of the '363 patent and Madaio.

The reasons for rejection are set forth in the Final Office Action of March 17, 2009 ("Final Action"), summarized as follows:

As set forth previously, Gaubitz, M., et al. teaches a method of treating lupus comprising extracorporeal column immunoadsorption of a subject's plasma for the removal of pathogenic antibodies. The reference further teaches that dsDNA-Ab play a "pivotal" role in the pathogenesis of SLE and that their removal proved useful for the treatment of the disease.

The reference teaching differs from the claimed invention only in that it does not teach a method employing a column comprising the R38 peptide nor the use of a Sepharose column.

The '363 patent teaches that the R38 peptide is derived from laminin and is recognized by pathogenic lupus antibodies. Madaio et al. teaches that dsDNA-Ab from lupus patients also recognize laminin.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to perform a method of treating lupus comprising extracorporeal column immunoadsorption of a subject's plasma for the removal of pathogenic antibodies, as taught by Gaubitz et al., employing the R38 peptide of the '363 patent. One of ordinary skill in the art at the time the invention was made would have been motivated to employ the R38 peptide on an immunoadsorption column given the teachings of Madaio et al. that

dsDNA-Ab from lupus patients also recognize laminin and the '363 patent that the R38 peptide is derived from laminin and is recognized by pathogenic lupus antibodies. Note that Claim 8 is included in the rejection because various types of immunoadsorber matrices (including Sepharose) for column chromatography were well-known in the art at the time of the invention. The choice of any particular immunoadsorber matrix would have comprised only routine optimization of the claimed method and would have been well within the purview of one of ordinary skill in the art at the time of the invention. Note that new claim 10 does not recite any new limitations because all ligands are coupled to Sepharose in some sort of coupling buffer.

As stated in the rejection, the extracorporeal column immunoadsorption of a subject's plasma for the removal of pathogenic antibodies was known in the art. Substituting a ligand known to bind said pathogenic antibodies for the ligand of the primary reference would have been expected function for the binding and removal of said pathogenic antibodies from the plasma.

Applicant argues unexpected results and further argues unexpected results need not be disclosed in the specification.

It is well established that the assertion of unexpected properties in the course of prosecution is not as persuasive as when said results are disclosed in the specification. As set forth in In re Davies and Hopkins 177 USPQ 381 (CCPA 1973), the court stated that evidence alleging unexpected properties need not be considered after filing because it properly belonged in the specification as filed: "There is no specific statutory requirement that compels applicant to disclose all properties of chemical compounds or compositions in his application; insofar as statute is concerned, only disclosure requirements are in first paragraph of 35 U.S.C. 112; however, public will derive the most benefit from a patent when it discloses on its face those properties or utilitarian advantages which were ultimately persuasive on question of nonobviousness".

While a case of prima facie obviousness can be rebutted by a showing of unexpected results, said results properly belong in the specification. Much the

same as in this case, the court stated: "Apparently it was only in the face of the rejections based on this art that appellants were moved to attempt to distinguish the properties obtained using the copolymer as a toughening agent versus using a homopolymer of butadiene". The court concluded: "Nevertheless, the public will derive the most benefit from a patent when it discloses on its face those properties or utilitarian advantages which were ultimately persuasive on the question of nonobviousness. However, when, as here, an applicant has satisfied the requirements of Section 112, we would be reluctant to require him to disclose more unless it could be done without prejudice to him. But if the applicant can be required to include the properties in his specification without prejudice to him, a compromise is reached upon which the evidentiary ruling can be based".

Further, a proper showing of unexpected results would also include both statistical evidence and a comparison to the most closely related prior art, neither of which are provided here.

The Inventor states in paragraph 8 that the claimed method has been performed on two patients and that in a single patient, "as shown in Figure 12, the level of anti-VRT (R38) antibodies decreased after the Luposorb apheresis and returned to the original levels after more than 5 weeks." In paragraph 10 the Inventor states, "As stated in paragraph 8 above, the continuing decline in antibody levels is an unusual and unexpected result, one that could not have been predicted from the disclosure of any of the references cited, nor any reference known to me".

A review of the data of Figure 12 reveals that it is not statistically significant and thus is of questionable probative value. Further, there is no comparison to the closest prior art and no showing that the decline in antibody levels is actually unexpected. Finally note that it appears that a rebound effect is demonstrated wherein antibody levels are actually higher at day 58 than they were pretreatment. If said data were to be found to be persuasive said data might necessitate a rejection for lack of enablement.

Applicant cites the additional 1.132 declaration of Inventor Naparstek of 12/10/07. The Inventor cites two references, Gokhale et al. and Grainger et al., to argue that an antibody rebound effect often follows plasmapheresis. The Inventor further argues that the rebound effect was not seen with the method of the instant claims.

As set forth in Grainger et al. the antibody rebound effect after the removal of all antibodies from a subject's plasma has been observed previously. Thus, sound scientific reasoning and common sense would dictate that improved plasmapheresis methods would seek to avoid this effect. Clearly, the concept of removing only pathogenic antibodies from a subject's plasma comprises the next logical step and does not require great insight. Thus, the claimed method would have been obvious to the ordinarily skilled artisan at the time of the invention.

The value of post-filing results submitted only in an attempt to overcome an obviousness rejection has been discussed above. Further regarding the instant results, however, it is unclear whether or not the antibody rebound effect is actually avoided with the method of the instant claims. Note that the effect was not seen in the patient of the Inventor's 9/17/07 declaration until day 58 post plasmapheresis. In the data of the instant declaration the post treatment antibody levels are disclosed only after one month. Accordingly, it is unclear what the antibody levels might rise to after two months or longer.

Applicant again argues unpredictable results citing additional results provided by the Inventor in a new 1.132. declaration, and states that a comparison to the closest prior art cannot be done.

Applicant's new results are noted, but given Applicant's incredible statement it is clear then that Applicant cannot demonstrate unpredictable results. Accordingly, the results cannot be considered to be sufficient to overcome the finding of obviousness. An attorney's mere statement that results are unexpected is not persuasive.

Applicant rejects the holdings in Davies and Hopkins and cites Knoll

v.Teva. Applicant may reject the court's holdings but they stand never the less. Regarding Knoll v. Teva, the fact pattern in the case is quite different from that in the instant case. First, the application did cite surprising results (which is not the case here). Second, the issue was technical in nature, i.e., whether or not a summary judgment by a district court was proper (it was not). Third, the court ruled regarding the new submission of unexpected results in "response to a litigation attack", not in the prosecution of a patent application. Finally, the court simply reversed and remanded the case to the district court for further review.

Regarding a more recent case, in one of the few obviousness cases post KSR Int'l. Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007), the court held in Leapfrog Enterprises Inc. v. Fisher-Price Inc., 82 USPQ2d 1687 (Fed. Cir. 2007) that even with a showing of "substantial" secondary considerations an invention can still be held to be obvious. Thus, in the instant case the combination of routine methods, that have been repeatedly and predictably employed for decades, is still obvious even in light of Applicant's asserted secondary unexpected results that Applicant states cannot be compared to the closest prior art and shown to actually be unexpected.

Applicant submits Hershko and Naparstek (2005) In support of the argument that in view of the prior art the method of the instant claims had no reasonable expectation of success.

The introduction of the reference teaches, "Until two decades ago, therapeutic plasma exchange was the only procedure used for antibody removal from the plasma", followed by a review of newer methods designed to remove only specific pathogenic antibodies. This teaching demonstrates that the removal of antibodies from the blood for the treatment of certain diseases is a very well-known concept. The reference continues by discussing the methods as they are used in the treatment of three diseases, MG, DCM, and SLE.

Applicant argues that treatment of MG by the removal of specific antibodies was unsuccessful. Applicant's position is acknowledged. However, a

review of the reference reveals that the apparent failure of the method in the context of MG was due to the low affinity of a single peptide for a single antibody. Contrast that with the successes in treating SLE. At page 637 the reference teaches that in one method anti-dsDNA complexes were eliminated and inflammation was ameliorated. Note that anti-dsDNA antibodies are the ligand for the R38 peptides employed in the method of the instant claims. Also see pages 640-641 wherein the authors teach that SLE can be effectively treated through the removal of anti-dsDNA antibodies, e.g., the quality of life of SLE patients improved due to a reduction in anti-dsDNA antibodies after being administered LJP394. Indeed, the reference supports the Examiner's position of obviousness in stating, "Peptide-bound columns allow specific removal of the pathogenic antibodies, implying that extracorporeal specific immunoadsorption on the laminin-epitope columns may serve as a new therapeutic alternative for SLE".

The position of the authors seems to be one of guarded optimism with the major concern being that pathogenic autoantibodies need to be identified before the method can be used. But fortunately, with SLE, pathogenic autoantibodies have been identified. The authors teach that it is the anti-dsDNA antibodies that are involved with renal disease that are pathogenic in the disease. While direct evidence might be lacking, the fact that the method of reducing levels of antidsDNA antibodies has been demonstrated to treat the disease is enough to render the method of the instant claims obvious in view of the prior art.

Applicant concludes by raising a number of possible issues that might render the claimed method ineffective. But note that none of these issues have been seen in the instant case. The r38 peptide does bind anti-dsDNA and countless peptides have been attached to columns for the purification of antibodies, indeed, the method is known as antibody affinity purification and it has been routine for decades. And regarding the final issue of plasma flow rate, the Hershko and Naparstek reference describes at least one type of column (Immunosorba) with a "nearly unlimited" adsorption capacity thus, even this

remote issue is really a non-issue.

B. The Prior Art

1. Gaubitz

Gaubitz discloses a comparison of two different immunoadsorption columns as treatment options for SLE. One of the columns uses phenylalanine, which removes antibodies by means of a non-specific affinity. The other column, the Ig-Therasorb™ column, contains polyclonal sheep antihuman antibodies directed against immunoglobulin kappa and lambda light chains and IgG heavy chains. The size of the sheep antibodies bound to the column is 150,000Da and they bind the Fc portion of human antibodies present in plasma. Both columns provide non-specific removal of all antibodies in a patient's plasma, not just removal of pathogenic antibodies. All patients admitted into the trials were on doses of non-steroidal anti-inflammatory drugs, corticosteroids and immunosuppressive drugs starting one month before treatment unto the end of the observation period. Results of the trials indicated that both columns were effective in lowering pathogenic antibodies and disease activity under persistent, unchanged immunosuppressant treatment. The clinical efficacy of immunoadsorption was good, and slightly superior to the published average percentage of responders on controlled plasmapheresis studies.

2. The '363 patent

The '363 patent, to the inventor of the subject application, Dr. Yaakov Naparstek, describes methods of treating SLE in patients having the disease, in which the R38 peptide, a peptide derived from the C-terminal region of the mouse laminin α chain and known to bind lupus antibodies, is directly administered to a patient, either orally, intravenously, or by other well-known mode of administration of pharmaceutical compositions.

3. Madaio

Madaio describes an investigation undertaken to determine the exact role of B cells and autoantibodies in the production of glomerular immune deposits, the location and quantity of which are linked to the severity of nephritis in SLE patients. In one aspect of the study, Madaio compared the incidence and severity of lupus nephritis in mice with and without B cell populations. All of the mice (using a strain that spontaneously develops SLE with nephritis) with B cells developed severe nephritis, while the knock-out mice, of the same strain but deficient in B cells, did not. This confirmed the role of B cells in the development of lupus nephritis.

It was known (prior to Madaio's study and reported by him at page 388, left column, first full paragraph) that serum levels of autoantibodies in patients without clinical evidence of disease could be markedly elevated, and conversely, are occasionally undetectable in patients with fulminant disease.

Madaio next examined the role of individual autoantibodies in the development of lupus nephritis. By comparing lupus serum autoantibodies to nephritogenic antibodies, it was found that the latter were enriched for autoreactivity for both intracellular and extracellular autoantigens. Madaio found extensive cross-reactivities among individual Ig, including reactivity to DNA, phospholipids, proteins and basement-membrane components such as heparan sulfate and laminin. In contrast, the cross-reactive antigen-binding properties of the serum autoantibodies derived from the same lupus mice were much more limited. These findings suggest that the specific antigen-binding region of the autoantibodies is influential in immune-deposit formation. Additional studies by Madaio confirmed the specificity of individual subset populations of lupus autoantibodies for specific intracellular and extracellular antigens. All of the studies conducted by Madaio were on mice.

C. Any Alleged Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Has Been Sufficiently Rebutted.

The Law of Obviousness and The Examiner's Argument

In order to establish a *prima facie* case of obviousness, an Examiner must articulate a sufficient reason why one skilled in the art would have modified the prior art to arrive at the presently claimed invention. This requirement is set forth in the MPEP at Section 2142 *et.seq.*, where the Supreme Court decision in *KSR v. Teleflex* is quoted:

> "The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. §103 should be made explicit. The Court quoting *In re Kahn,* 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396."

Even after the heightened standard established by the Supreme Court in *KSR,* it is still the case, stated in the MPEP at Section 2143, that claims may only be rejected as *prima facie* obvious so long as there is a reasonable expectation of success in combining elements of the prior art. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). While obviousness does not require absolute predictability, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); MPEP 2143.02. Evidence of lack of expectation of success and unexpected results can be used to rebut the *prima facie* case asserted by the Examiner. MPEP 2143.02.

The Examiner asserts that it would be *prima facie* obvious to use a column such as Therasorb™, taught by Gaubitz, substituting the specific antigen R38 (as taught in the '363 patent) in place of the non-specific antigen to remove only lupus-specific antibodies, as in the methods of the present

invention. In Appellant's view, the Examiner refuses to give adequate consideration to 1) the differences between the present invention and the prior art; 2) the data presented in the declarations of Dr. Naparstek, including evidence of unexpected results; and 3) evidence of failure of others. All of these together point to a lack of predictability or expectation of success and are sufficient to overcome any so-called *prima facie* case of obviousness. Appellant addresses each of these factors in turn, and respectfully requests reconsideration.

1. Differences between the cited prior art and the present invention.

There are many significant differences between the methods of the present invention and the disclosure of the references, and of Gaubitz in particular. The R38 peptide is less than 3,000 Da in size (only twenty-one amino acids in length), and binds only to lupus-specific antibodies, which are less than 1% of all antibodies present in an SLE patient's plasma. In contrast, the sheep antibodies in the Therasorb column described in Gaubitz are 150,000 Da in size, and bind to all human antibodies. In the methods of the present invention, the specific antibody-antigen (R38 – anti-R38 antibody) interaction is targeted in the separation column. This specific interaction is not shown in the two adsorption columns compared in Gaubitz, nor shown in any of the other adsorption columns described in Gaubitz at page 2, first column. Thus, the present invention differs from the teachings of Gaubitz in that 1) the specific R38 – anti-R38 antibody interaction is used as the basis for separation, 2) only lupus specific antibodies are removed from plasma, 3) the size of the ligand on the column differs substantially from that shown in Gaubitz, and 4) the concentration of specific antibodies removed in relationship to the total concentration of antibodies in plasma is different. All of these factors influence the ability of a plasmapheresis treatment protocol to successfully remove only a small fraction of antibodies from a patient's plasma while the patient is connected to the machine.

Gaubitz may be considered the closest prior art, as it discloses a method of treating SLE using plasmapheresis, albeit a method distinct from that of the present invention, as noted above. As noted in Gaubitz, the patients were give concomitant immunosuppressive therapy to prevent a rebound effect. The other references do not teach methods of extracorporeal removal of lupus-specific antibodies at all, and are merely cited for their disclosure of the relationship of the R38 peptide to laminin, and the knowledge that lupus autoantibodies bind to R38 and laminin (and in the case of Madaio, mouse, not human antibodies. In sum, there are no references cited by the Examiner showing extracorporeal methods of removing antigen-specific antibodies for treatment of any disease. Contrary to the assertion of the Examiner that the invention "combines routine methods that have been repeatedly and predictably employed for decades", the present invention is the first method of treatment of SLE using extracorporeal removal of only lupus specific-autoantibodies, and is one of the first attempts at antigen-specific extracorporeal removal of antibodies in the treatment of disease (discussed further below under "Failure of Others").

2. Expectation of Success

Appellant does not deny that antibody-antigen interactions, *in general,* are well-characterized, and also acknowledges that as a general proposition anti-R38 antibodies would be expected to bind to R38. The Examiner's assertion that "there is nothing novel regarding the removal of specific antibodies from a solution employing a column comprising an antibody's antigen.... [and] has been a routine laboratory practice for decades" overlooks the important fact that Appellant's method is not a laboratory method; it is a method of treating a patient. Most methods of plasmapheresis do not simply remove plasma from a patient in a "batch mode", run it through a column in a laboratory, and return the plasma to the patient.

Appellant respectfully submits that there was no expectation of success

in the methods of treatment of the present invention, despite the well-known antibody-antigen relationship. For example, there was no guarantee that the same binding shown on an ELISA plate (as described in the '363 patent) will occur in a column, due to conformational changes in the protein when attached to a substrate, particularly a protein that is only twenty-one amino acids in length. One skilled in the art could not predict, based on the teachings of Gaubitz, that the specific R38 – anti-R38 antibody interaction would provide the basis for a successful method of treatment in SLE, given

1) the small size of the R38 protein,

2) possible changes in conformation due to binding on a substrate,

3) possible differences in antibody-antigen affinity of the R38-antiR38 antibody combination as compared to the sheep antibody/Fc system of Therasorb™,

4) the very low level of anti-R38 antibodies in plasma, and

5) the plasma flow rate required to make this method of treatment viable.

Conveniently, the unpredictability of the entire system is overlooked and/or completely disregarded in the obviousness determination.

3. Evidence of Unexpected Results

It is asserted in the Final Rejection that the data presented in the Second and Fourth Declarations of Dr. Naparstek are insufficient to show unexpected results, due to an alleged lack of statistical significance, among other things. It is further asserted that evidence of unexpected results must appear in the specification as filed to be properly considered. Appellant strongly disagrees with these assertions.

In the Second Declaration of Dr. Naparstek Appellant submitted findings on one patient, indicating success in treatment and an unexpected continued decline in serum lupus autoantibody levels through day 14. In the Fourth Declaration of Dr. Naparstek findings on ten additional patients were submitted. In seven of the ten patients shown in the Fourth Declaration, the

treatment regimen was successful, and no rebound effect was observed. These results are, in fact, statistically significant ($p<.01$), as indicated in Figure 11 in the declaration. The patient data shown in Figures 1, 7, 8, 9, 10, 11 also exhibit a continued decline in autoantibody levels measured post-treatment.

The patients who were successfully treated in the study did not have a rebound effect. The rebound effect is described in the Third Declaration of Dr. Naparstek, with citations to journal articles explaining this well-known phenomenon. When antibodies are removed by plasmapheresis, a rebound effect occurs, usually within 7-10 days (see Reference 2 in the Fourth Declaration), and serum levels of antibodies spike higher than the levels measured just prior to the plasmapheresis treatment.

It is asserted by the Examiner that "sound scientific reasoning and common sense would dictate that improved plasmapheresis methods would seek to avoid this [rebound] effect. Clearly, the concept of removing only pathogenic antibodies from a subject's plasma comprises the next logical step and does not require great insight". It is a correct statement that improved plasmapheresis methods are continually being sought, including those provided by the methods of the present invention. However, there is no scientific basis or rationale provided for the Examiner's inference that removal of only pathogenic antibodies will avoid the rebound effect. Removal of pathogenic antibodies alone *could have* induced a rebound in the levels of pathogenic antibodies. On the other hand, the opposite *could have* happened, and this was what, in fact, was observed in the present invention. No reference or citation to other scientific fact was provided for the assertion that it was entirely predictable that no rebound would occur.

The results of the patient study indicate that, contrary to the expectations of the inventor, as attested to in the Third Declaration, the treatment methods of the invention worked, and further showed an unexpected decline in serum autoantibody levels post-treatment.

It is asserted by the Examiner that the continued decline of antibody

levels post-treatment is not unexpected. However, no other explanation is offered, nor is there any citation to literature or other evidence to support the assertion that this result was predictable. The Examiner simply responds "Applicant asks the Examiner to explain his data". As with many other assertions in the Office Action, these are the Examiner's conclusory statements made without any factual foundation whatsoever.

Finally, it is asserted in the Final Rejection that evidence of unexpected results must "properly appear in the specification" and can therefore be disregarded if not in the application as filed. Citation to *In re Davies and Hopkins*, 177 USPQ 381 (CCPA 1973) is provided as support for this position.

Appellant strongly disagrees with the Examiner's position and submits that the Examiner's reliance on this case is far outside the mainstream of standard patent practice. A more recent case, reaching the opposite conclusion, is *Knoll Pharmaceutical Co. v. Teva Pharmaceuticals USA, Inc.*, 367 F.3d 1381, 1385, 70 USPQ2d 1957 (Fed. Cir. 2004), where the Federal Circuit stated ``There is no requirement that an invention's properties and advantages were fully known before the patent application was filed ... .''. Indeed, in *Knoll* the patentee was permitted to submit evidence of unexpected results at the time of trial to rebut the obviousness challenge. The Examiner points to distinctions between *Knoll* and the present situation. However, the fact remains that there is no language in *Knoll* limiting the holding of the case, as it pertains to presentation of unexpected results, to the narrow factual situation presented in that case.

It is well established in patent practice that evidence of unexpected results may submitted in a declaration filed under Rule 1.132 during prosecution, as set forth in the MPEP Section 716. An entire section of the MPEP is devoted to this subject (declarations under Rule 1.132). MPEP 716.01 states that "Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted prior to a final rejection" and in several other circumstances. This is also set forth at

MPEP Section 2141, Examination Guidelines for Determining Obviousness under 35 USC §103, where it is written:

> Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. *Graham v. John Deere Co.*, 383 U.S. at 17-18, 148 USPQ at 467 (1966). Such evidence, sometimes referred to as "secondary considerations," may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. The evidence may be included in the specification as filed, accompany the application on filing, or be provided in a timely manner at some other point during the prosecution. The weight to be given any objective evidence is made on a case-by-case basis.

As recently as December 2008, in Sanofi-Synthelabo v. Apotex, Inc., the Federal Circuit permitted patentee to present evidence of nonobviousness at trial in a challenge to the validity of a patent under §103.

Accordingly, the Examiner is obligated to consider evidence of unexpected results submitted during prosecution, and yet has failed to do so.

4. Failure of Others

In connection with the Response filed just prior to the Final Rejection, Appellant submitted an article entitled "Removal of Pathogenic Auto-antibodies by Immunoadsorption" ("the Hershko paper"). The publication date of this article is June, 2005, after the filing date of the present application. It was written by Alon Hershko and Yaakov Naparstek, the inventor on the application which is the subject of this appeal.

This article provides specific support for the proposition that one skilled in the art cannot determine, *a priori*, if methods of **treatment** using extracorporeal immunoadsorption to remove specific autoantibodies will successfully treat the disease. As set forth in this article at page 639, first full paragraph, the authors note that in the treatment of myasthenia gravis, attempts at selective removal of one class of autoantibodies, those specific to

the alpha-67-76 sequence (the alpha subunit) of the Ach receptor protein were unsuccessful, due to the low affinity of peptides containing this sequence to the autoantibodies, even when conformation changes were introduced in the peptides to improve their antigenicity. The following paragraph goes on to state that "the specificity of the technique, which is its major advantage, proved to be a significant drawback because the anti-AChR blocking antibody is merely one subpopulation among several others implicated in the pathogenesis of MG." The cited paper, endnote 30, was published in December, 2001, after the filing date of the present application.

The only other antigen-specific removal of pathogenic autoantibodies discussed in the Hershko paper is the use of this method in the treatment of cardiomyopathy, described at pp. 639-640 and cited in endnote 41. This study was published in 2002, after the filing date of the present invention.

Thus, of the three known treatment methods based on antigen-specific removal of pathogenic antibodies, one being the present invention (and two of which were published after the filing date of the present application), two worked (including the present invention) and one did not.

The Examiner dismisses the findings of the Hershko paper with the following analysis:

> Applicant's position is acknowledged. However, a review of the reference reveals that the apparent failure of the method in the context of MG was due to the low affinity of a single peptide for a single antibody. *Contrast that with the successes in treating SLE* (emphasis added). At page 637 the reference teaches that in one method anti-dsDNA complexes were eliminated and inflammation was ameliorated. Note that anti-dsDNA antibodies are the ligand for the R38 peptides employed in the method of the instant claims. Also see pages 640-641 wherein the authors teach that SLE can be effectively treated through the removal of anti-dsDNA antibodies, e.g., the quality of life of SLE patients improved due to a reduction in anti-dsDNA antibodies after being administered LJP394. Indeed, the reference supports the Examiner's position of obviousness in stating, "Peptide-bound columns allow specific removal of the pathogenic antibodies, implying that extracorporeal specific

immunoadsorption on the laminin-epitope columns may serve as a new therapeutic alternative for SLE".

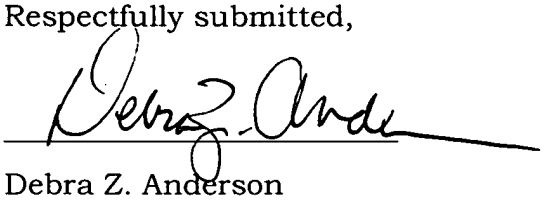
Indeed, the reference speaks optimistically about success in treating SLE because it is referring to the inventor's success in the present invention, and does not in any way support the Examiner's position. Apparently, the publication date of this reference was overlooked. Again, the Examiner refuses to give adequate (or any) consideration to evidence provided by Appellant.

Appellant respectfully submits that in view of the differences between the invention and the prior art, the lack of predictability, the evidence of unexpected results, and the failure of others, any so-called *prima* facie case of obviousness has been overcome. Withdrawal of the §103 rejection is respectfully requested.

CONCLUSION

Appellant respectfully submits that all pending claims, Claims 8-13, are patentable and that the present application is in condition for allowance; such action is respectfully requested at an early date.

Respectfully submitted,



Debra Z. Anderson
Registration No. 44,506
Attorney for Appellant
Meyer Unkovic & Scott
530 Smithfield Street
Suite 1300
Pittsburgh, PA 15219
412.456.2818

CLAIMS APPENDIX

8. The method of Claim 9, wherein the column is a N-hydroxysuccinimide (NHS-) – activated highly cross linked 4% agarose column.

9. A method of treating a subject having systemic lupus erythematosus comprising extracorporeal treatment of plasma from the subject by affinity adsorption column chromatography, wherein the column comprises a peptide having an amino acid sequence as set forth in SEQ. ID. NO. 1, and returning plasma so treated to the subject.

10. The method of Claim 9, wherein the peptide is coupled to the column using a coupling buffer.

11. A method of treating a subject having systemic lupus erythematosus comprising extracorporeal treatment of plasma from the subject by affinity adsorption column chromatography, wherein the column consists essentially of a peptide having an amino acid sequence as set forth in SEQ. ID. NO. 1, and returning plasma so treated to the subject.

12. The method of Claim 11, wherein the peptide is coupled to the column using a coupling buffer.

13. The method of Claim 11, wherein the column is a N-hydroxysuccinimide (NHS-) – activated highly cross linked 4% agarose column.

EVIDENCE APPENDIX

1. First Declaration of Dr. Yaakov Naparstek, signed June 19, 2005 and filed in connection with the Response to Office Action dated June 22, 2005, and entered into the record as noted in the Office Action dated January 1, 2006.

2. Second Declaration of Dr. Yaakov Naparstek, signed September 17, 2007, and filed in connection with the Request for Continued Examination dated September 24, 2007, and entered into the record as noted in the Office Action dated December 31, 2007.

3. Third Declaration of Dr. Yaakov Naparstek, signed December 10, 2007 and filed in connection with the post-interview Supplemental Response dated December 10, 2007, and entered into the record as noted in the Office Action dated December 31, 2007.

4. Fourth Declaration of Dr. Yaakov Naparstek, signed June 29, 2008 and filed in connection with the Response to Office Action dated June 29, 2008, and entered into the record as noted in the Office Action dated September 17, 2008.

RELATED PROCEEDINGS APPENDIX

None.

Docket No. 56040-B/JPW/GJG/DJK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Yaakov Naparstek

Serial No. : 09/826,069 Examiner: G.R. Ewoldt

Filed : April 4, 2001 Group Art Unit: 1644

For : PEPTIDES FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS AND METHODS OF TREATING SYSTEMIC LUPUS ERYTHEMATOSUS

1185 Avenue of the Americas
New York, New York 10036

Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

Sir:

DECLARATION OF YAAKOV NAPARSTEK UNDER 37 C.F.R. 61.132

I, Yaakov Naparstek, hereby declare as follows:

1. I am the inventor of the subject matter claimed in the above-identified patent application.

2. I have prepared a sterile 50 ml R-38-Sepharose column for specific extracorporeal immunoadsorption for SLE patients. 5 ml samples of the R-38-Sepharose beads were used to test their ability to remove anti-R-38 lupus antibodies. The lupus antibodies were transferred on the column and the flow-through fractions were tested for binding to R-38 by ELISA.

3. 61-86% of the lupus antibodies were removed as shown in Table 1 below.

Table 1 - R-38 Binding of SLE Antibodies[1]

Antibodies	Pre column	After immunoadsorption	% reduction of O.D.
C72 Antibody[2] (AntiDNA)	1.613	0.21	86.2%
SLE patient[3] D.A.	0.928	0.359	61.2%

(1) Measured by O.D. 405 in an ELISA test.
(2) 100 ml of the monoclonal mouse anti DNA antibody C72 were transferred on a 5 ml sample from a 50 ml R-38 Sepharose column. The R-38 binding was reduced from 1.613 to 0.21 after adsorption.
(3) Plasma from an SLE patient D.A. was diluted 1:100. Four ml filtered plasma was put on the R-38 column. The binding was reduced from 0.925 to 0.359.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Yaakov Naparstek 19/6/05
Yaakov Naparstek Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Naparstek, Yaakov

Serial No. : 09/826,069

Filed : April 4, 2001

For : PEPTIDES FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS AND METHODS OF TREATING SYSTEMIC LUPUS ERYTHEMATOSUS

Group Art Unit: 1644
Examiner: EWOLDT G. R.

Tel-Aviv, Israel
September 17, 2007

Hon. Commissioner of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450
Sir:

DECLARATION UNDER 37 CFR SEC 1.132

I, the undersigned (inventor), Yaakov Naparstek, of 17 Davidson St., Jerusalem, Israel, hereby declare as follows:

Background Information

1. I obtained an MD degree in 1973, from the Hadassah-Hebrew University Medical School in Jerusalem, Israel.

2. I am employed at Hadassah University Hospital, Jerusalem, Israel, as Chairman of Medicine and as Professor of Medicine at the Hebrew University - Hadassah School of Medicine, Jerusalem, Israel.

3. I am Board certified in Internal Medicine, Rheumatology and Clinical Immunology and Allergy.

4. I have been a research fellow and a visiting Professor at the Weizmann Institute of Science, Rehovot, Tuft's University, Boston, The National Institute of Health, Bethesda and Stanford University, Stanford. I now serve as the Director of the Hadassah Clinical Immunology and Rheumatology Center.

5. I am also the incumbent of the Leifferman Chair in Rheumatology.

6. My main research interests are in the field of autoimmunity, SLE and autoimmune arthritis. In recent years, my research group has focused on the identification of the target antigens in SLE and in autoimmune arthritis and in the attempts to develop antigen-specific therapeutic modalities to those diseases.

7. I am the recipient of national and international awards, and the author of about 100 publications and chapters in books as well as many patents in the field of autoimmune inflammatory diseases.

8. Under my direction and control the following experiment is being undertaken, which has been approved by the Internal Review Board (Helsinki) and by the Israeli Ministry of Health:

Phase I/II Clinical Trial with Luposorb™ Immunoadsorption Columns in Systemic Lupus Erythematosus (SLE or lupus) patients

10 SLE patients will be recruited for treatment with a single Luposorb™ immunoadsorption session during routine plasmapheresis procedure. The Luposorb™ immunoadsorption column is an affinity adsorption column comprising R38 (VRT101) peptide. Patient screening prior to enrollment into the study is between 4 weeks up to 7 days prior to the day planned for plasmapheresis. Patients will be enrolled into the study on the plasmapheresis day and will undergo treatment of between 2-3 hours with the Luposorb™ column. The patients will then be followed up for 8 weeks after the Luposorb™ column procedure.

As of yet, two patients underwent treatment and completed the two-month follow-up period. The attached chart refers to the first patient only. The procedure was well-tolerated and no procedure-related adverse events were detected in either patient. As to preliminary efficacy, Figure 12 depicts the changes in antibody levels of the patient before treatment, after treatment and during the follow-up period. As shown in Figure 12, the level of anti-VRT (R38) antibodies decreased after the Luposorb™ apheresis and returned to the original levels after more than 5 weeks.

Overview Statement

9. The explanations contained in the following paragraphs address the uniqueness of the present invention over prior art solutions. The explanations do not replace the detailed background and technical details that were already provided in the patent application. These explanations are brought here to challenge the relevance of the Examiner's rejection statements, as stated in the Office Action (OA) dated January 30, 2006 and September 8, 2006.

10. As stated in paragraph 8 above, the continuing decline in antibody levels is an unusual and unexpected result, one that could not have been predicted from the disclosure of any of the references cited, nor any reference known to me.

11. I believe that the Examiner's rejection of the claims based on obviousness is overcome with the evidence of unexpected results.

12. This declaration is given in support of the patent prosecution efforts in the present application, before the USPTO.

13. I declare that all the statements made herein of my own knowledge are true, and that all statements made on information and knowledge are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 17 day of Sept 2007.

Yaakov Naparstek

417257-v2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	: NAPARSTEK, Yaakov
Serial No.	: 09/826,069
Filed	: April 4, 2001
For	: PEPTIDES FOR THE TREATMENT OF : SYSTEMIC LUPUS ERYTHEMATOSUS : AND METHODS OF TREATING : SYSTEMIC LUPUS ERYTHEMATOSUS : : Group Art Unit 1644 : Examiner: G. EWOLDT

Hon. Commissioner of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR SEC 1.132

I, the undersigned, Yaakov Naparstek, of 17 Davidson St., Jerusalem, Israel, hereby declare as follows:

1. Previous methods of treating systemic lupus erythematosus (SLE) include plasmapheresis, which has been used since 1974. In plasmapheresis a patient's plasma is separated from the blood cells and either discarded and replaced with substitute donor plasma or filtered with standard equipment and returned to the patient. All immune complexes and antibodies are thus removed from a patient's blood.

It is well known that treatment of patients with plasmapheresis must be followed by cyclophosphamide, for example, or other immunosuppressive drugs due to the rebound effect, in which the body compensates for the removal of antibodies by producing an overabundance of antibodies, leading to other deleterious side effects.

See, e.g., the enclosed articles, both of which document the rebound effect:

1. "Plasmapheresis: an adjunct therapy in severe progressive neuropsychiatric lupus.", *J. Assoc. Physicians India*, 2001 Oct; 49:986-9; and
2. "Immunoadsorption therapy (Therasorb) in patients with severe lupus erythematosus", *Acta Med. Austriaca*, 2002;29:26-29. Numerous other articles available on the internet document the rebound effect. Thus, plasmapheresis is only a moderately successful treatment for SLE at best, and in fact in several studies it has been shown to be no better than treatment with cyclophosphamide alone (see footnotes 17, 18 and 19 in Reference 2).

2. A newer therapy, described in Reference 2 above, is a type of immunoadsorption, in which a patient's blood is removed from the body and passed through a column which contains antibodies (such as sheep antibodies) which will bind human antibodies and remove them from the blood. Again, the removal is non-specific, i.e., all antibodies are removed, and there is concern about the rebound effect. In the study described in Reference 2, intravenous immunoglobulin was administered to the patients to avoid the rebound effect (see page 27, top paragraph of the right hand column). This therapy also has other disadvantages, such as the fact that the blood must be passed through the column numerous times (18 cycles) in order to accomplish a significant removal of antibodies.

The Gaubitz article, J. Autoimmunity (1998) 11, 495-501, cited as prior art by the Examiner in the captioned application, describes a comparison of the Therasorb column with another type of immunoadsorption column. The article does not discuss a rebound effect, but this could be due to concomitant immunosuppressive therapy (see table 2 and p. 500, left column, bottom paragraph).

3. In the present invention, extracorporeal removal of only lupus-specific antibodies from the plasma of SLE patients is accomplished by means of an adsorption column containing the R38 laminin peptide. This peptide specifically binds lupus antibodies and removes them from the plasma of a patient. In contrast to the other treatment methods described above, no rebound effect was observed in the patient data referred to in connection with the last declaration. A graph showing antibody levels in two patients pre- and one month post-treatment by methods of the present invention was inadvertently omitted with the last declaration, and it is included herewith. One of the patients did not receive any immunosuppressive treatment, while the other one received only low doses of corticosteroids and azathiorpine at the time of treatment with the methods of the present invention.

4. It is my well-considered opinion that the present invention is not obvious in view of any of the cited references, alone or in combination. It was completely unpredictable, and completely unexpected, that the present invention would work as described and overcome the obstacles and deleterious side effects shown in prior art treatment methods for SLE.

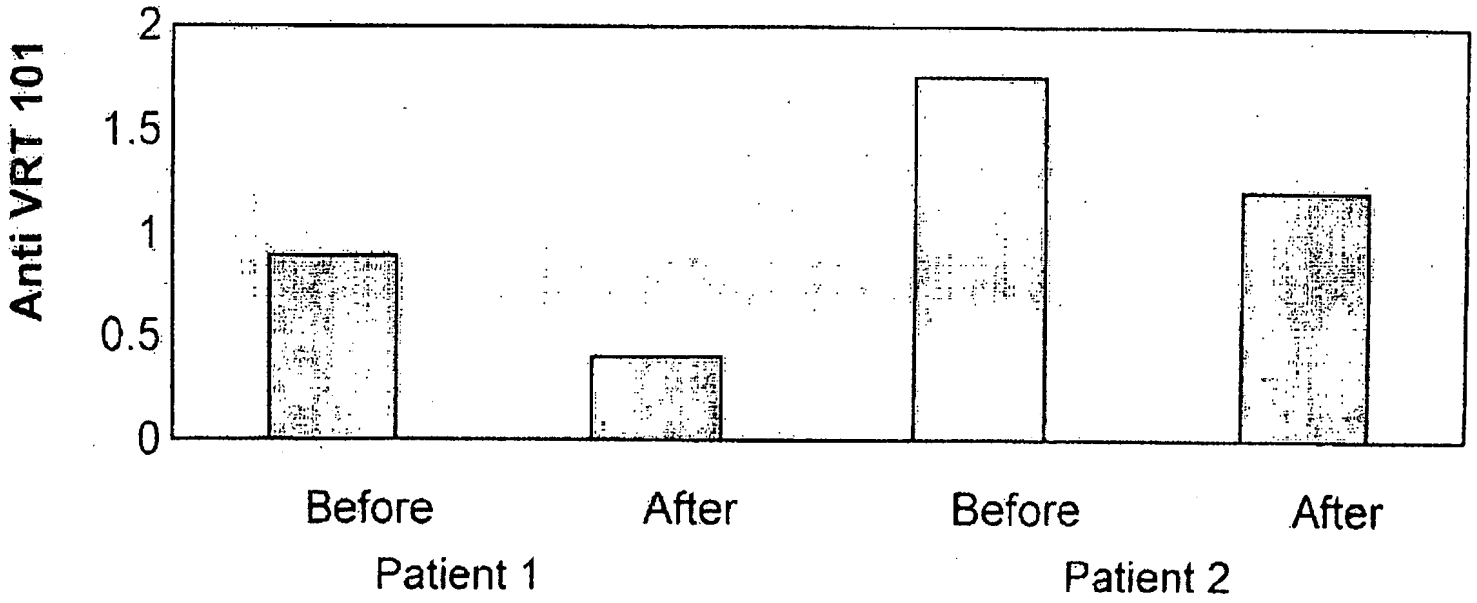
5. I declare that all the statements made herein of my own knowledge are true, and that all statements made on information and knowledge are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 10 day of December 2007.

Yaakov Naparstek

Figure 1

Anti VRT level- before and one month after apheresis on the Lupusorb column



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	: NAPARSTEK, Yaakov
Serial No.	: 09/826,069
Filed	: April 4, 2001
For	: PEPTIDES FOR THE TREATMENT OF : SYSTEMIC LUPUS ERYTHEMATOSUS : AND METHODS OF TREATING : SYSTEMIC LUPUS ERYTHEMATOSUS : : Group Art Unit 1644 : Examiner: G. EWOLDT

Hon. Commissioner of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

June 30, 2008

DECLARATION UNDER 37 CFR SEC 1.132

I, the undersigned, Yaakov Naparstek, of 17 Davidson St., Jerusalem, Israel, hereby declare as follows:

Background Information

1. I obtained an MD degree in 1973, from the Hadassah-Hebrew University Medical School in Jerusalem, Israel.

2. I am employed at Hadassah University Hospital, Jerusalem, Israel, as Chairman of Medicine and as Professor of Medicine at the Hebrew University – Hadassah School of Medicine, Jerusalem, Israel.

3. I am Board certified in Internal Medicine, Rheumatology and Clinical Immunology and Allergy.

4. I have been a research fellow and a visiting Professor at the Weizmann Institute of Science, Rehovot, Tuft's University, Boston, The National Institute

of Health, Bethesda and Stanford University, Stanford. I now serve as the Director of the Hadassah Clinical Immunology and Rheumatology Center.

5. I am also the incumbent of the Leifferman Chair in Rheumatology.

6. My main research interests are in the field of autoimmunity, SLE and autoimmune arthritis. In recent years, my research group has focused on the identification of the target antigens in SLE and in autoimmune arthritis and in the attempts to develop antigen-specific therapeutic modalities to those diseases.

7. I am the recipient of national and international awards, and the author of about 100 publications and chapters in books as well as many patents in the field of autoimmune inflammatory diseases.

8. Under my direction and control the following trials were undertaken, which has been approved by the Internal Review Board (Helsinki) and by the Israeli Ministry of Health:

Phase I/II Clinical Trial with Lupusorb™ Immunoadsorption Columns in Systemic Lupus Erythematosus (SLE or lupus) patients

Ten additional SLE patients were recruited for treatment with a single Lupusorb™ immunoadsorption session during routine plasmapheresis procedure. The Lupusorb™ immunoadsorption column is an affinity adsorption column comprising R38 (VRT101) peptide. Patient screening prior to enrollment into the study was between 4 weeks up to 7 days prior to the day planned for plasmapheresis. Patients were enrolled into the study on the plasmapheresis day and underwent treatment of between 2-3 hours with the Lupusorb™ column. The patients were then followed up for 8 weeks after the Lupusorb™ column procedure. Patients continued on any drug regimen that had been in place prior to the trial, but no drugs such as cyclophosphamide were administered to combat a potential rebound effect. No rebound effect was observed.

Figures 1-10 document the findings in each of the ten patients. In most patients, anti-R38 antibodies declined immediately after treatment, and remained low at visit 4, four weeks post-treatment. In the 3 patients shown in Figures 3, 4 and 6, anti-R38 antibody levels were not reduced by the treatment.

Figure 11 is a summary chart of the findings in all 10 patients. Mean anti-VRT values, including p values ($p=0.009$ for visit 1 and 3), are reported in the chart.

9. I declare that all the statements made herein of my own knowledge are true, and that all statements made on information and knowledge are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 29 day of July 2008.

Yaakov Naparstek

Figure 1

Patient #002

Anti- VRT - Serum					
Visit #	Date Sample Received	Test Date	OD 405		Average
			Duplicate 1	Duplicate 2	
Visit 1 (Pre)	6.3.07	7.3.07	0.87	0.779	0.88
Visit 1 (post)	6.3.07	7.3.07	0.627	0.611	0.62
Visit 2	20.3.07	26.3.07	0.174	0.183	0.15
Visit 3	25.3.07	26.3.07	0.19	0.197	0.16
Visit 4	10.4.07	13.4.07	0.403	0.416	0.408
Visit 5	3.5.07	9.5.07	1.389	1.411	1.4

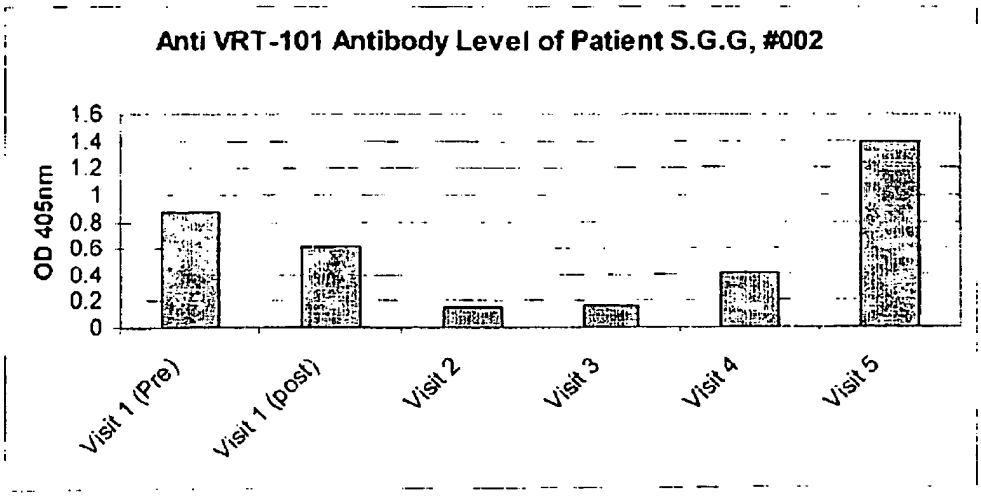


Figure 2

Patient #003

Anti-VRT - Serum					
Visit #	Date Sample Received	Test Date	OD 405		Average
			Duplicate 1	Duplicate 2	
Visit 1 (Pre)	21.5.07	21.5.07	1.816	1.696	1.756
Visit 1 (post)	21.5.07	21.5.07	1.939	1.792	1.8655
Visit 2	7.6.07	14.6.07	1.151	0.843	0.997
Visit 3	14.6.07	14.6.07	1.111	1.253	1.182
Visit 4	20.6.07	21.6.07	1.167	1.233	1.2
Visit 5	17.7.07	18.7.07	0.823	0.826	0.8245

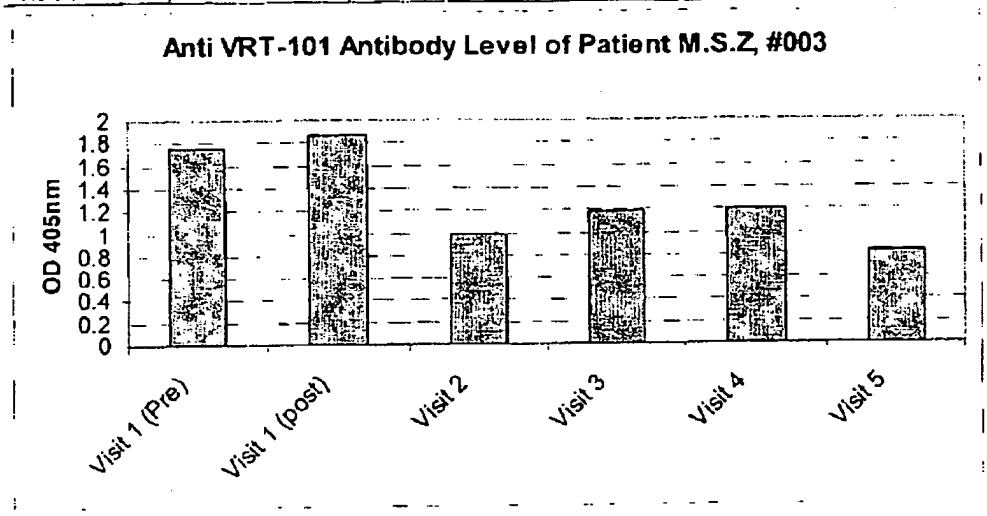


Figure 3

Patient #013

Anti- VRT - Serum					
Visit #	Date Sample Received	Test Date	OD 405 Duplicate 1	OD 405 Duplicate 2	Average
Visit 1 (Pre)	31.10.07	4,6.11.07	1.075	1.135	1.105
Visit 1 (post)	31.10.07	4,6.11.07	0.809	0.826	0.8175
Visit 2	15.11.07	19.11.07	1.251	1.329	1.29
Visit 3	22.11.07	26.11.07	1.231	1.01	1.1205
Visit 4	29.11.07	3.12.07	1.72	2.077	1.8985
Visit 5	27.12.07	31.12.07	1.285	1.294	1.2895

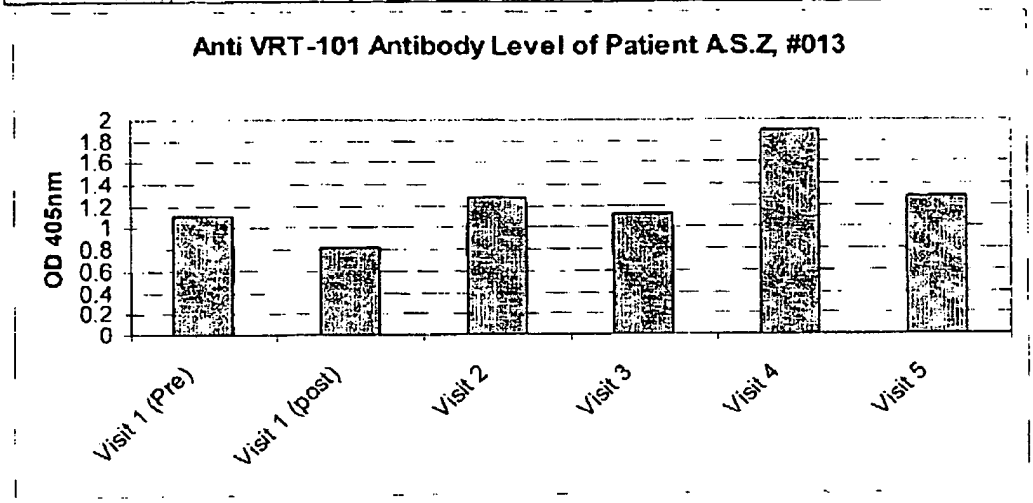


Figure 4

Patient #014

Anti- VRT - Serum					
Visit #	Date Sample Received	Test Date	OD 405		Average
			Duplicate 1	Duplicate 2	
Visit 1 (Pre)	29.11.07	3.12.07	0.491	0.678	0.5845
Visit 1 (post)	29.11.07	3.12.07	0.42	0.365	0.3925
Visit 2	11.12.07	13.12.07	0.559	0.662	0.6105
Visit 3	17.12.07	19.12.07	0.622	0.571	0.5965
Visit 4	25.12.07	31.12.07	0.637	0.736	0.6865
Visit 5	30.1.08	4.2.08	0.433	0.475	0.454

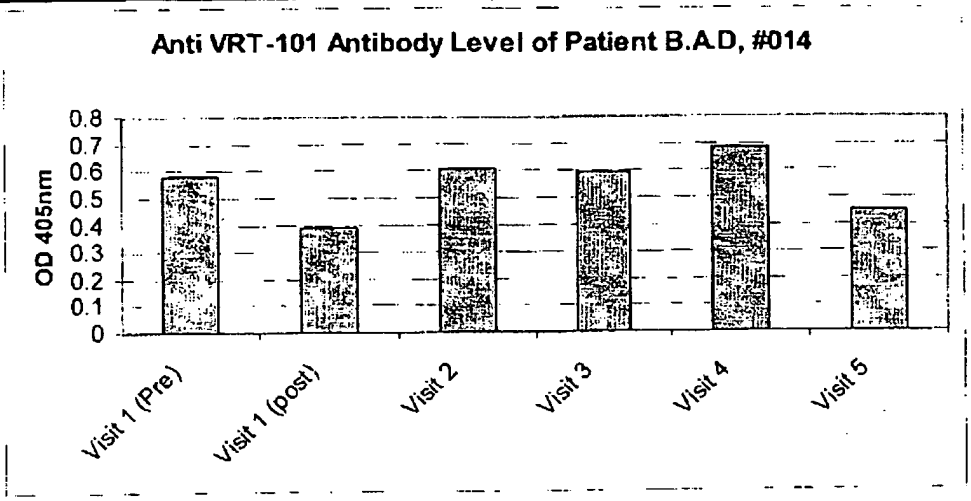


Figure 5

Patient #024

Anti-VRT - Serum

Visit #	Date Sample Received	Test Date	OD 405		Average
			Duplicate 1	Duplicate 2	
Visit 1 (Pre)	9.1.08	10.1.08	0.556	0.462	0.509
Visit 1 (post)	9.1.08	10.1.08	0.357	0.356	0.3565
Visit 2	21.1.08	27.1.08	0.61	0.6	0.605
Visit 3	29.1.08	4.2.08	0.285	0.304	0.2945
Visit 4	5.2.08	6.2.08	0.166	0.304	0.235
Visit 5	4.3.08	12.3.08	0.342	0.507	0.4245

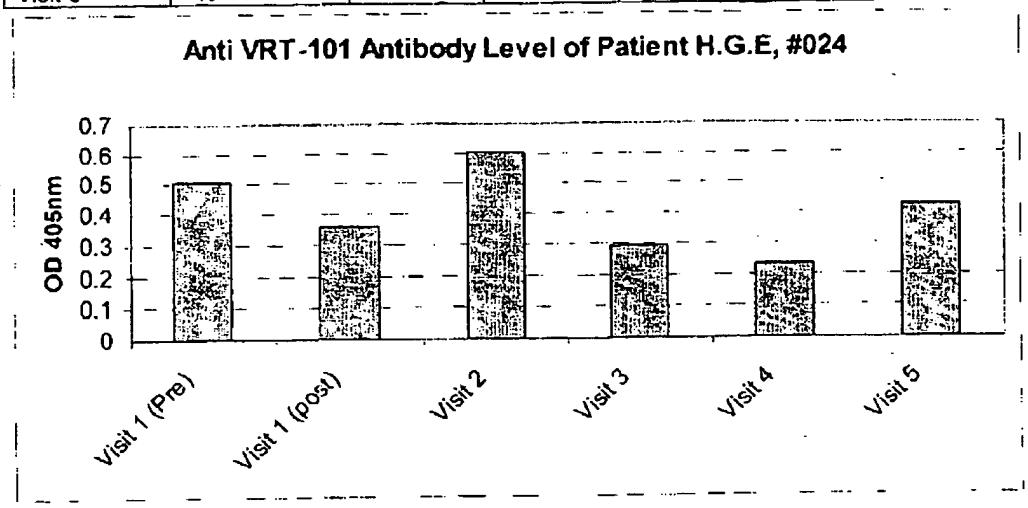


Figure 6

Patient Initial: Patient #027

Anti- VRT - Serum

Visit #	Date Sample Received	Test Date	OD 405		Average
			Duplicate 1	Duplicate 2	
Visit 1 (Pre)	27.2.08	2.3.08	0.339	0.498	0.4185
Visit 1 (post)	27.2.08	2.3.08	0.412	0.361	0.3865
Visit 2	10.3.08	12.3.08	0.405	0.443	0.424
Visit 3	17.3.08	18.3.08	0.2235	0.537	0.38025
Visit 4	26.3.08	30.4.08	0.454	0.517	0.4855
Visit 5	5.5.08	5.5.08	0.386	0.325	0.3555

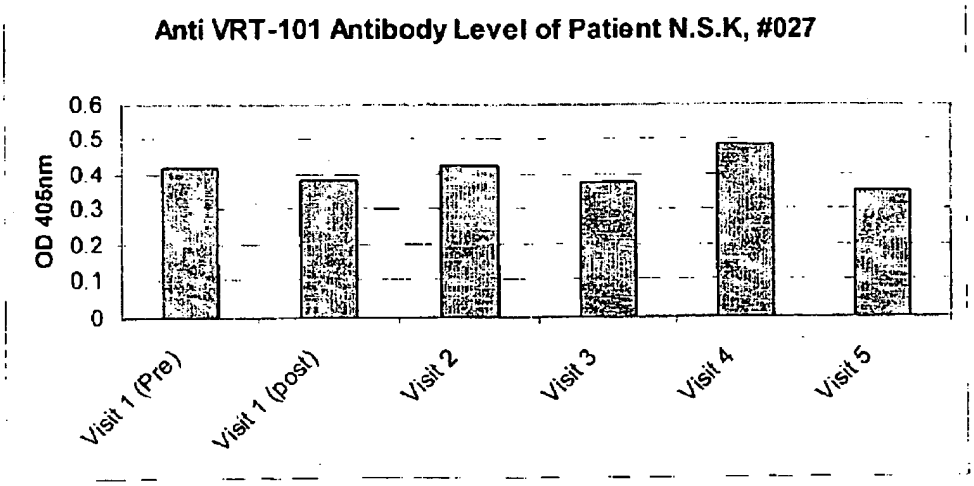


Figure 7

Patient Initial: Patient #037

Anti- VRT –Serum					
Visit #	Date Sample Received	Test Date	OD 405		Average
			Duplicate 1	Duplicate 2	
Visit 1 (Pre)	25.3.08	25.3.08	1.04	0.981	1.0105
Visit 1 (post)	25.3.08	25.3.08	0.632	0.4	0.516
Visit 2	1.4.08	1.4.08	0.39	0.455	0.4225
Visit 3	9.4.08	9.4.08	0.348	0.358	0.353
Visit 4	15.4.08	15.4.08	0.394	0.361	0.3775
Visit 5	13.5.08	22.5.08	0.276	0.309	0.292

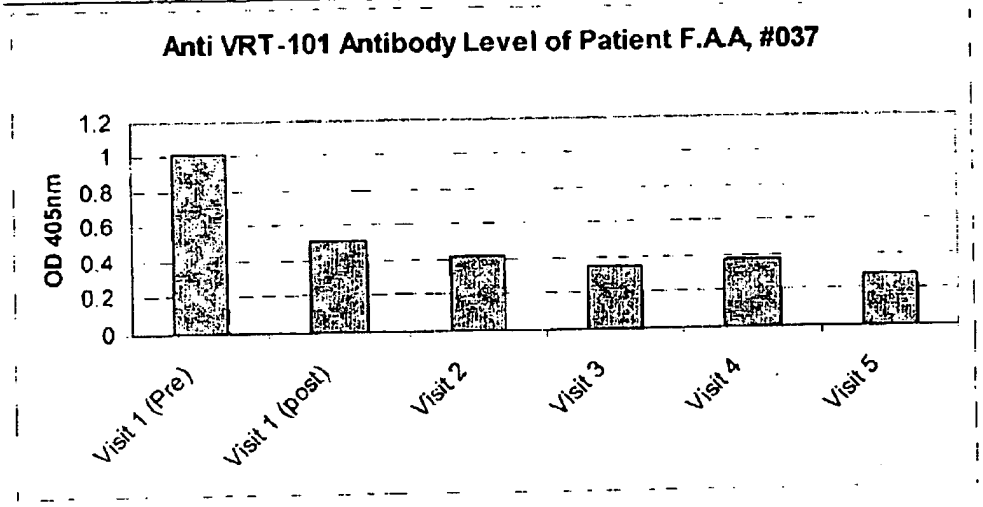


Figure 8

Patient Initial: Patient #030

Anti-VRT - Serum					
Visit #	Date Sample Received	Test Date	OD 405		Average
			Duplicate 1	Duplicate 2	
Visit 1 (Pre)	25.3.08	25.3.08	0.429	0.528	0.4785
Visit 1 (post)	25.3.08	25.3.08	0.345	0.306	0.3255
Visit 2	1.4.08	1.4.08	0.287	0.337	0.312
Visit 3	9.4.08	9.4.08	0.214	0.2	0.207
Visit 4	15.4.08	15.4.08	0.316	0.223	0.2695
Visit 5	13.5.08	22.5.08	0.218	0.214	0.216

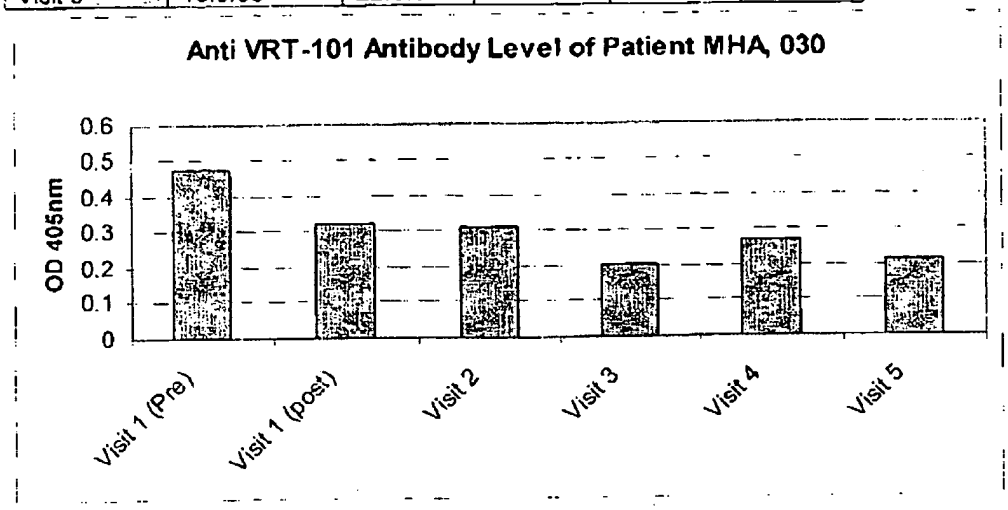


Figure 9

Patient Initial: Patient #031

Anti- VRT - Serum

Visit #	Date Sample Received	Test Date	OD 405		Average
			Duplicate 1	Duplicate 2	
Visit 1 (Pre)	26.3.08	26.3.08	0.315	0.342	0.3285
Visit 1 (post)	26.3.08	26.3.08	0.303	0.344	0.3235
Visit 2	1.4.08	1.4.08	0.235	0.321	0.278
Visit 3	9.4.08	9.4.08	0.137	0.153	0.145
Visit 4	15.4.08	15.4.08	0.207	0.198	0.2025
Visit 5	13.5.08	22.4.08	0.163	0.175	0.169

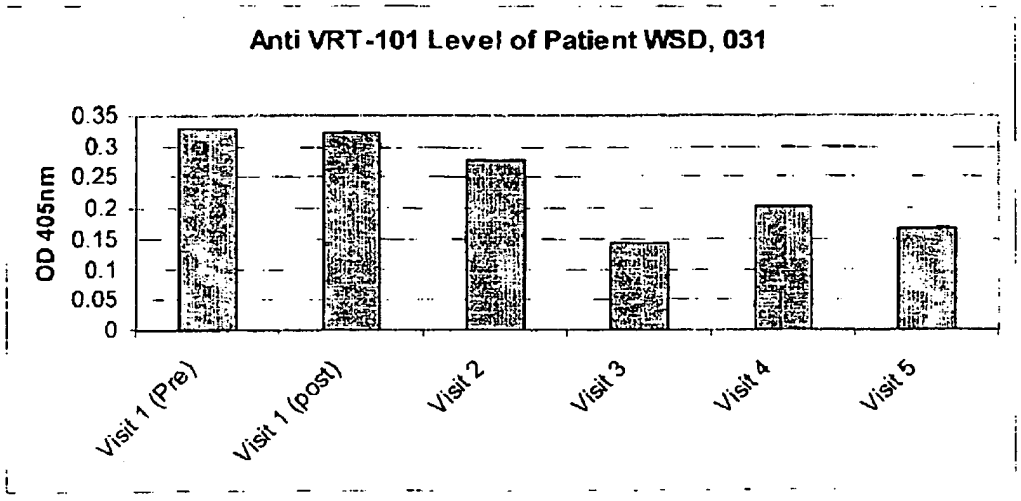


Figure 10

Patient Initial: Patient #040

Anti- VRT - Serum					
Visit #	Date Sample Received	Test Date	OD 405		Average
			Duplicate 1	Duplicate 2	
Visit 1 (Pre)	1.4.08	1.4.08	0.741	1.032	0.8865
Visit 1 (post)	1.4.08	1.4.08	0.7	0.693	0.6965
Visit 2	9.4.08	9.4.08	0.235	0.239	0.237
Visit 3	15.4.08	15.4.08	0.394	0.361	0.3775
Visit 4	5.5.08	5.5.08	0.356	0.454	0.405
Visit 5	21.5.08	28.5.08	0.472	0.539	0.506

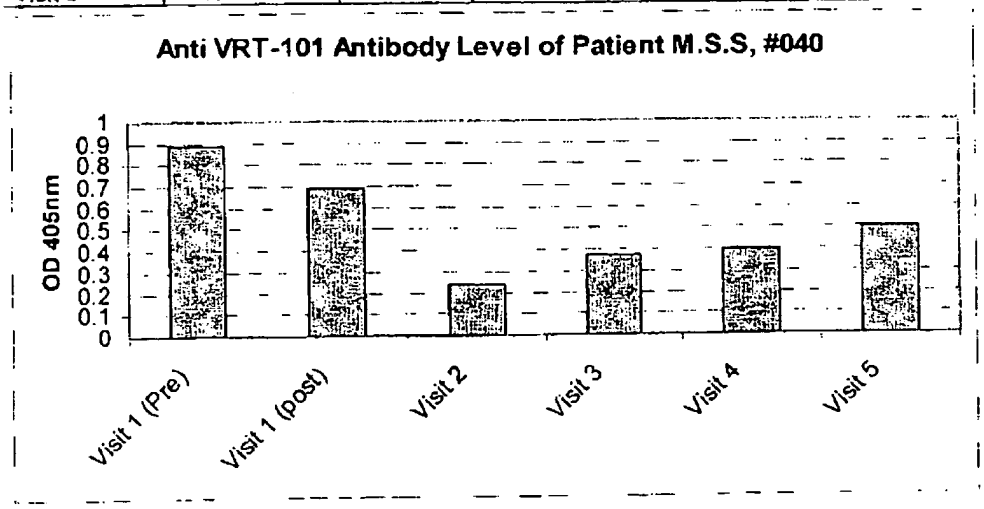


Figure 11: Anti-VRT 101 Antibody Levels After Lupusorb™ Apheresis